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(71) Applicant: MEDIVIR AB [SE/SE]; Lunastigen 7, S–141 44 Huddinge (SE).

(72) Inventors: LEANNA, M., Robert; 1025 Popes Creek Circle, Grayslake, IL 60030 (US). HANNICK, Steven, M.; 2285 Linden Avenue, Highland Park, IL 60035 (US). RASMUSSEN, Michael; 1256 Sheridan Road, Kenosha, WI 53140 (US). TIEN, Jien–Heh, J.; 1287 North Maidstone Drive, Vernon Hills, IL 60061 (US). BHAGAVATULA, Lakshmi; 205 Sheffield Lane, Vernon Hills, IL 60061 (US). SINGAM, Pulla, Reddy; 690 Dursey Lane, Des Plaines, IL 60016 (US). GATES, Bradley, D.; 18 Audrey Lane, Mount Prospect, IL 60056 (US). KOLACZKOWSKI, Lawrence; 5822 Constitution Avenue, Gurnee, IL 60031 (US). PATEL, Ramesh, R.; 3131 West Fargo Avenue, Chicago, IL 60645 (US). WAYNE, Greg; 88 Jansson Lane, Vernon Hills, IL 60061 (US). LANNOYE, Greg; 33425 Lone Rock Road, Wildwood, IL 60030 (US). ZHANG, Weijiang; 389 Ashford Lane, Grayslake, IL 60030 (US). LUKIN, Kirill, A.; 50 Parliament Way, Mundelein, IL 60060 (US). NARAYANAN, Bikshandarkor; 31 Sherwood Court, Mundelein, IL 60060 (US). RILEY, David, A.; 5904 80th Place, Kenosha, WI 53142 (US). MORTON, Howard; 6088 Indian Trail Road, Gurnee, IL 60031 (US). CHANG, Sou–Jen; 16139 West Port Clinton Road, Prairie View, IL 60069 (US). CURTY, Cynthia, B.; 18011 Banbury Drive, Gurnee, IL 60031 (US). PLATA, Daniel; 14265 West Shelley Lane, Wadsworth, IL 60083 (US). BELLETTINI, John; 1380 S. White Oak Drive #1422, Waukegan, IL 60085 (US). SHELLAT, Bhadra; 1041 Breckenridge, Lake Forest, IL 60045 (US). SPITZ, Tiffany; 666 Central Avenue, Highland Park, IL 60035 (US). YANG, Cheng–Xi; 1216 Heatherfield, Glenview, IL 60025 (US).

(74) Agent: MORRISON, Iain; Medivir AB, Lunastigen 7, S–141 44 Huddinge (SE).

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(54) Title: SYNTHESIS OF ACYCLIC NUCLEOSIDE DERIVATIVES

(57) Abstract

Novel intermediates and improvements in the synthesis of acyclic guanine nucleoside prodrugs of the formula (R)–9–[(2–alkanoylmethyl)–4–(aminoacyloxy)butyl]guanine (for example valtamociclovir stearate), including purine salts amenable to one pot alkylation with the acyclic side chain, acyclic 2–amino–6–halo–purine and protected guanine precursors, one pot manipulations thereof and last step work up procedures.

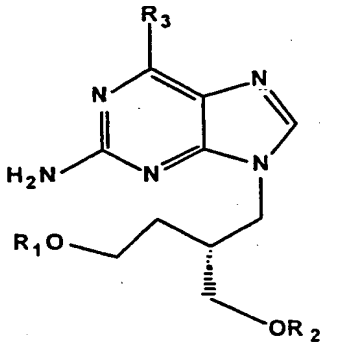
Synthesis of Acyclic Nucleoside Derivatives

Technical Field

This invention relates to the field of acyclic nucleosides and in particular to the synthesis of compounds useful against herpes and retroviral infections and novel intermediates therefore.

Background of the invention

International patent applications WO97/30051 and WO97/30052, both published 21 August 1997 the contents of which are hereby incorporated by reference, describe the preparation and antiviral activity of certain acyclic nucleosides of the formula I:



I

wherein

a) R_1 is -C(O)CH(CH(CH_3)$_2$)NH_2 or -C(O)CH(CH(CH_3)CH_2CH_3)NH_2 and R_2 is -C(O)C_3-C_{21} saturated or monounsaturated, optionally substituted alkyl; or

b) R_1 is -C(O)C_3-C_{21} saturated or monounsaturated, optionally substituted alkyl and R_2 is -C(O)CH(CH(CH_3)$_2$)NH_2 or -C(O)CH(CH(CH_3)CH_2CH_3)NH_2; and R_3 is OH or H.

International patent application no WO 98/34917, the contents of which are hereby incorporated by reference and which was published on13 August

Most preferred compounds of the formula I are those where R_1 is -$C(O)CH(CH(CH_3)_2)NH_2$ or -$C(O)CH(CH(CH_3)CH_2CH_3)NH_2$ and R_2 is -$C(O)C_9$-C_{17} saturated alkyl.

The term "lower alkyl" as used herein refers to straight or branched chain alkyl radicals containing from 1 to 7 carbon atoms including, but not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl, n-pentyl, 1-methylbutyl, 2,2-dimethylbutyl, 2-methylpentyl, 2,2-dimethylpropyl, n-hexyl and the like.

The term "alkanoyl" as used herein refers to $R_{20}C(O)$- wherein R_{20} is a loweralkyl group.

The term "alkoxy" as used herein refers to $R_{21}O$- wherein R_{21} is a loweralkyl group.

The term "alkoxyalkyl" as used herein refers to an alkoxy group appended to a loweralkyl radical.

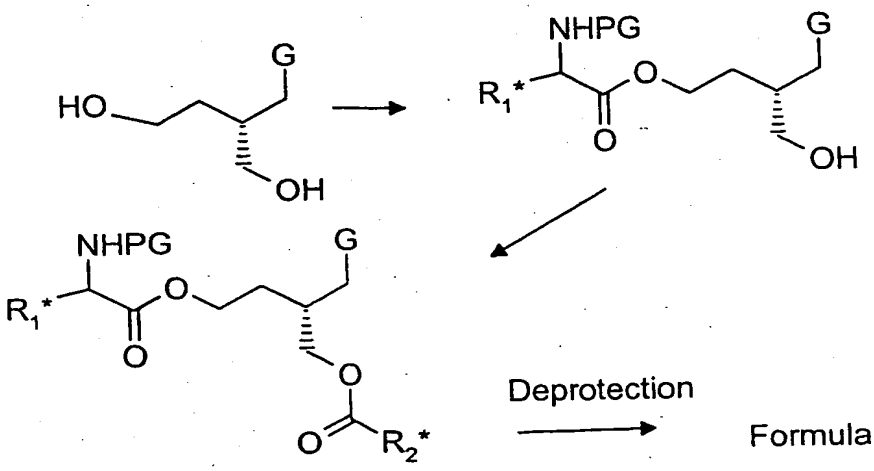
The term "N-protecting group" or "N-protected" as used herein refers to those groups intended to protect the N-terminus of an amino acid or peptide or to protect an amino group against undesirable reactions during synthetic procedures. Commonly used N-protecting groups are disclosed in Greene, "Protective Groups in Organic Synthesis" (John Wiley & Sons, New York, 1981), which is hereby incorporated by reference. N-protecting groups include acyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoracetyl, trichloroacetyl, phthalyl, o-nitrophenoxyacetyl, -chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and the like; sulfonyl groups such as benzenesulfonyl, p-toluenesulfonyl, and the like, carbamate forming groups such as benzyloxycarbonyl, p-chlorobenzyloxy-carbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyl-oxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxy-carbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenylyl)-1-

The compounds of Formula I may be isolated as the hydrate. The compounds of the invention may be isolated in crystal form, preferably homogenous crystals, and thus an additional aspect of the invention provides the compounds of Formula I in substantially pure crystalline form, comprising >70%, preferably >90% homogeneous crystalline material, for example >95% homogeneous crystalline material.

The compounds of Formula I may be prepared from H2G as described in the documents above, namely Schemes A and B.

A. Direct acylation method

Scheme A

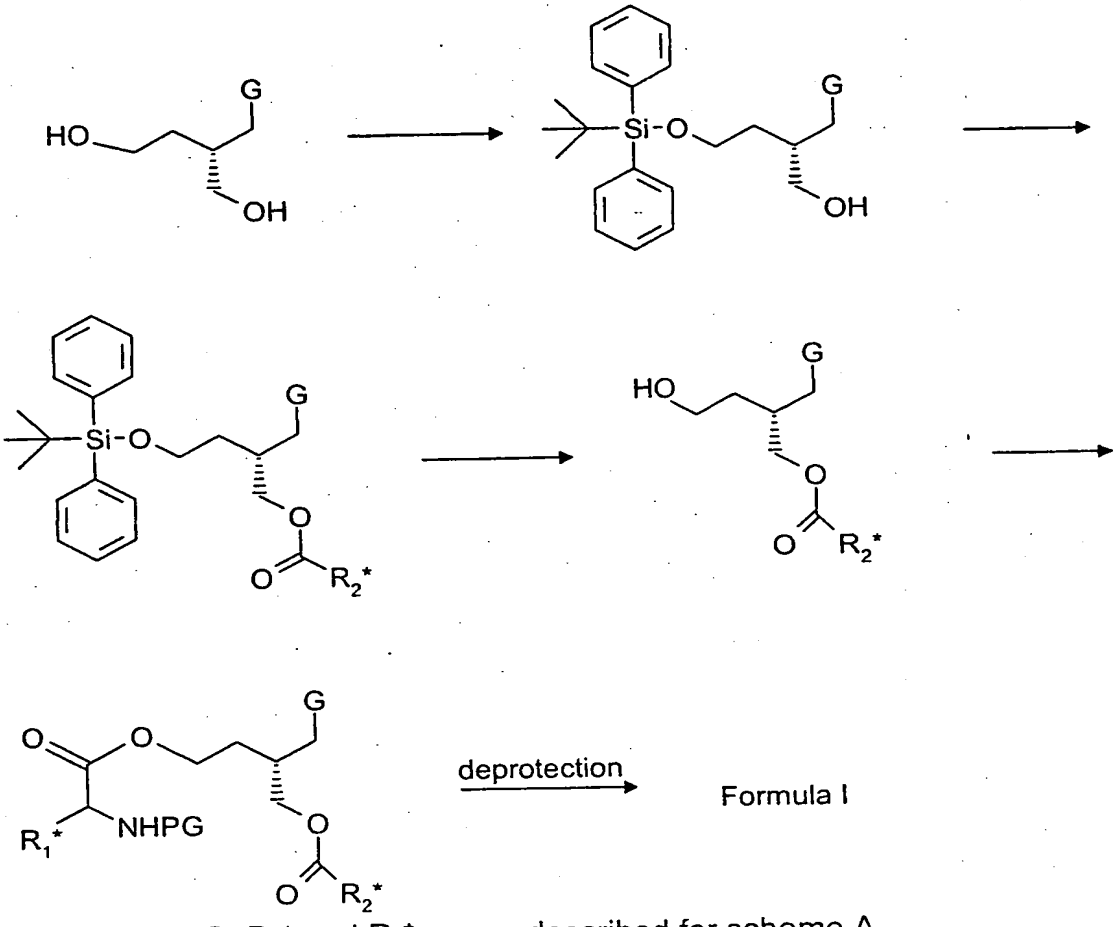


Scheme A depicts the preparation of compounds in which R_1 is derived from the amino acid and R_2 is derived from the fatty acid, but the converse scheme is applicable to compounds where R_1 is derived from the fatty acid and R_2 is derived from the amino acid ester. In the variant specifically depicted in scheme A above, G is guanine or 6-deoxyguanine, PG is an optional N-protecting group

each case represents the corresponding R_1/R_2 amino acid or the R_1/R_2 fatty acid. Representative activated acid derivatives include the acid chloride, formic and acetic acid derived mixed anhydrides, anhydrides derived from alkoxycarbonyl halides such as isobutyloxycarbonylchloride and the like, N-hydroxysuccinamide derived esters, N-hydroxyphthalimide derived esters, N-hydroxy-5-norbornene-2,3-dicarboxamide derived esters, 2,4,5-trichlorophenol derived esters and the like.

B. Via protection of the side chain 4-hydroxy group:

Scheme B



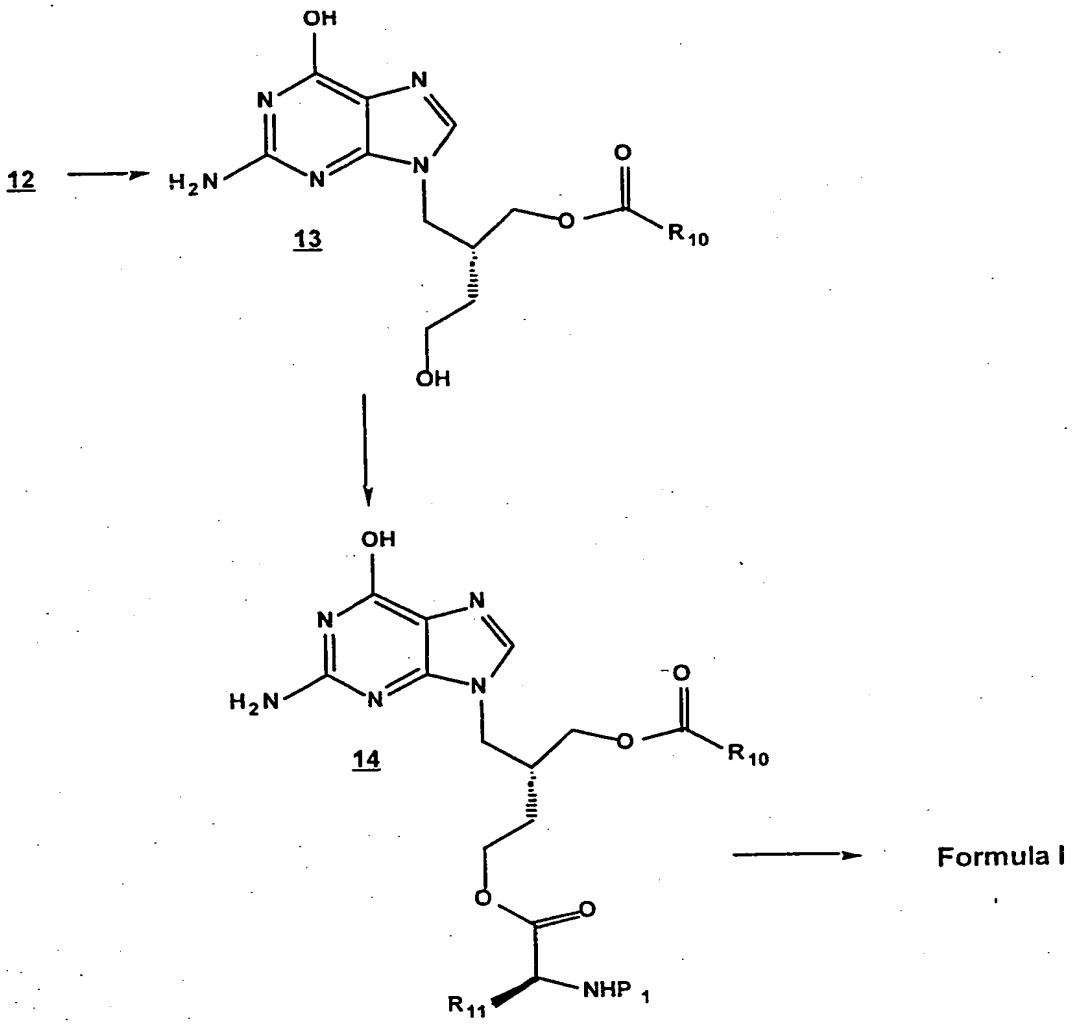
Formula I

wherein G, PG, R_1* and R_2* are as described for scheme A.

Additional techniques for introducing the fatty acid ester of R_1/R_2, for instance in the schemes herein include the enzymatic route described in Preparative Biotransformations 1.11.8 (Ed S M Roberts, J Wiley and Son, NY, 1995) with a lipase such as SP 435 immobilized Candida antarcticus (Novo Nordisk), porcine pancreatic lipase or Candida rugosa lipase. Enzymatic acylation is especially convenient where it is desired to avoid N-protection and deprotection steps on the other acyl group or the purine 2-amine.

The invention particularly relates to novel intermediates and improvements in the synthesis schemes C, D and E disclosed in the international patent applications described above.

SCHEME C cont'd



Referring to Scheme C, malonate 1 (R_4 and R_5 are lower alkyl or benzyl or the like) is alkylated by reaction with from about 0.5 to about 2.0 molar equivalents of acetal 2 (R_6 and R_7 are lower alkyl or benzyl and the like or R_6 and R_7 taken together are $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$ or $-CH_2CH_2CH_2CH_2-$and X_1 is a leaving group (for example, Cl, Br or I, or a sulfonate such as methanesulfonate,

triethylamine or potassium carbonate or pyridine or dimethylaminopyridine or ethyldiisopropylamine and the like) in an inert solvent (for example methylene chloride or toluene or ethylacetate or pyridine or methyl t-butyl ether and the like) at a temperature of from about -25°C to about 100°C to provide ester **7** (X_2 is a halogen or sulfonate leaving group).

Reaction of **7** with from about 0.9 to about 2.0 molar equivalents of 2-amino-6-chloropurine **8** in the presence of from about 1.0 to about 6.0 molar equivalents of a base (for example, potassium carbonate **or LiH** or NaH or KH or NaOH or KOH or lithium diisopropylamide or $LiN(Si(CH_3)_3)_2$ and the like) in an inert solvent (for example, DMF or THF or acetonitrile or N-methylpyrrolidone or ethanol or DMSO and the like) at a temperature of from about -25 °C to about 140°C provides substituted purine **9**.

Alternatively, the base can be a sterically bulky amine base (for example, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,4-diazabicyclo[2.2.2]octane (Dabco), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), tetramethylguanidine, N,N-diisopropylethylamine and the like) or a sterically bulky phosphazine base (for example, tert-butylimino-tri(pyrrolidino)-phosphorane, tert-butylimino-tri(dimethylamino)phosphorane, tert-octylimino-tri(dimethylamino)phosphorane and the like) in an inert solvent (for example, THF or DMF or DMSO and the like).

Alternatively Mitsunobu coupling (for example $P(Ph)_3$/diethyl azidocarboxylate) of alcohol **6** with 2-amino-6-chloropurine **8** provides **9**.

Reaction of **9** with from about 2.0 to about 20 molar equivalents of an alcohol R_9OH (R_9 is an alcohol protecting group such as benzyl or diphenylmethyl and the like) in the presence of from about 1.0 to about 6.0 molar equivalents of a base (for example, potassium t-butoxide or potassium carbonate or NaH or KH or lithium diisopropylamide and the like) in an inert solvent (for example, THF or DMF and the like) at a temperature of from about -25°C to about 150°C provides alcohol **10**.

borohydride or RaNi/H_2 or borane t-butylamine complex and the like) at a temperature of from about -25 °C to about 100°C to provide alcohol **13**. The optical purity of compound **13** can be enhanced by reaction with optically active oraganic sulfonic acids such as (S)-(+)-camphorsulfonic acid and the like. A preferred sulfonic acid for this purpose is (S)-(+)-camphorsulfonic acid.

Alternatively, the acetal substituent of **12** can be hydrolyzed by reaction in an inert solvent with an acid resin (for example, Amberlyst 15 resin, Nafion NR50 resin, Dowex 50WX4-200R resin or Amerlite 120 resin and the like) to provide the corresponding aldehyde. The aldehyde can be isolated prior to reduction to the alcohol **13** as described above or the crude aldehyde can be reduced directly *in situ*.

Reaction of **13** with from about 0.8 to about 3.0 molar equivalents of N-protected amino acid $P_1NHCH(R_{11})COOH$ or an activated derivative thereof (P_1 is an N-protecting group (for example, benzyloxycarbonyl, t-butyloxycarbonyl, allyloxycarbonyl and the like) and R_{11} is isopropyl or isobutyl) in an inert solvent (for example, THF or dioxane or dioxolane or DMF or methylene chloride and the like) at a temperature of from about 25°C to about 100°C provides alcohol **14**.

N-deprotection of **14** provides the compound of the invention of formula **I** wherein R_3 is -OH. For example, when the protecting group can be removed by hydrogenation, such as when the protecting group is Cbz, hydrogenation in the presence of Pd/C in ethanol or Pd/$BaCO_3$ or Pd/$BaSO_4$ and the like in THF or isopropanol/THF and the like is preferred.

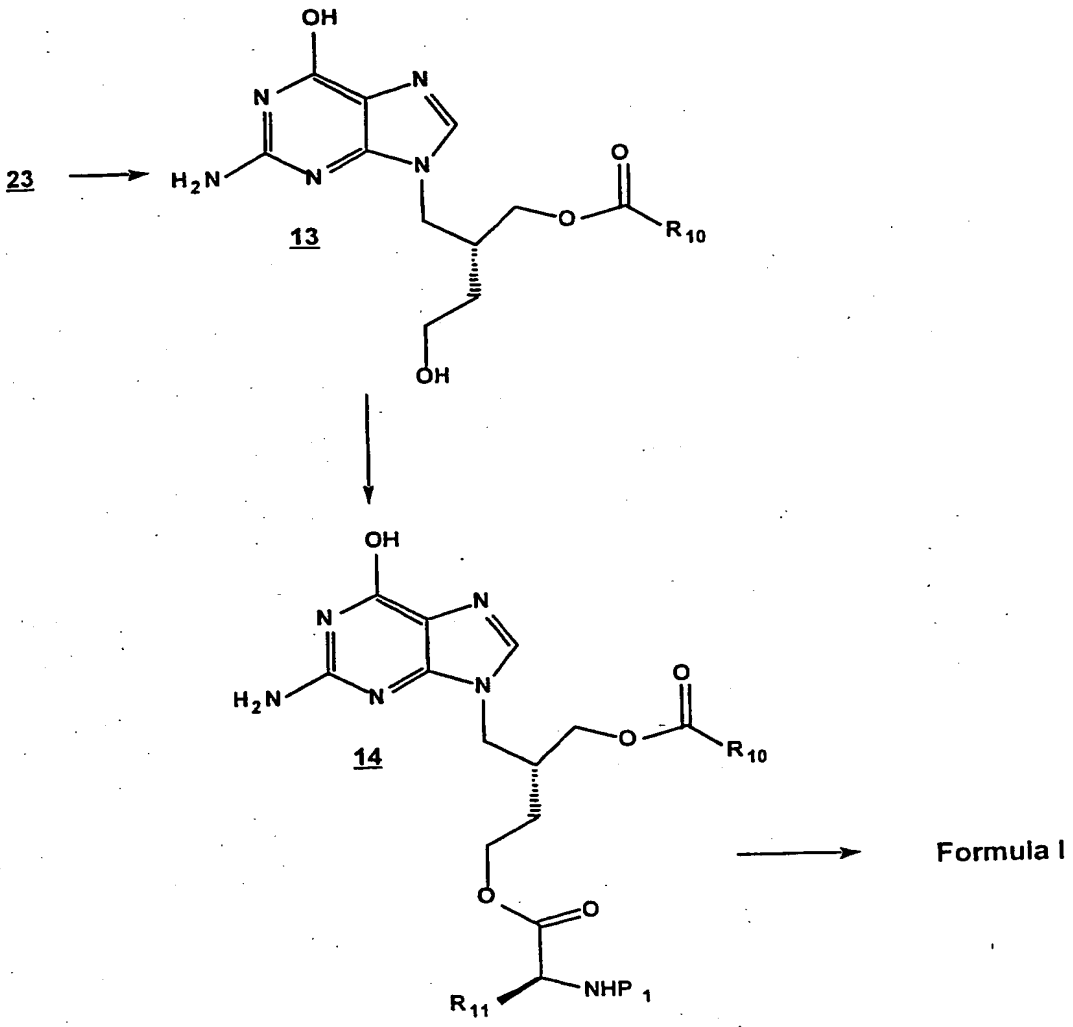
Alternatively, compound **13** can be reacted with the symmetrical anhydride derived from $P_1NHCH(R_{11})COOH$ (i.e., $P_1NHCH(R_{11})C(O)O\text{-}C(O)CH(R_{11})NHP_1$) to provide **14**. The anhydride can be prepared *in situ* or can be separately prepared prior to reaction with **13**.

Alternatively, **11** can be prepared by hydrolysis of the ester of **9** to an alcohol (for example, by reaction with a base such as K_2CO_3, Li_2CO_3, Na_2CO_3, $KHCO_3$, LiOH, NaOH or KOH and the like in an inert solvent such as methanol,

In yet another alternative, **13** can be prepared from **11** without isolation of intermediates and with *in situ* generation of the esterification agent, thus increasing purity of the resulting product and allowing increased throughput in the process.

Another alternative process for the preparation of compounds of Formula I wherein R_3 is -OH is shown in Scheme D.

SCHEME D cont'd



Malonate 1 (R_4 and R_5 are lower alkyl or benzyl and the like) is alkylated with from about 0.5 to about 2.0 molar equivalents of ether 15 wherein X_1 is a leaving group (for example Cl, Br or I, or a sulfonate such as methane sulfonate, triflate, p-toluenesulfonate, benzenesulfonate and the like) and R_{12} is $-CH(Ph)_2$, $-C(Ph)_3$ or $-Si(t\text{-}Bu)(Me)_2$ and the like (Ph = phenyl) in the presence of from about

ether and the like) at a temperature of from about -25°C to about 100°C to provide ester **19** (X_2 is a halogen or sulfonate leaving group).

Reaction of **19** with from about 0.9 to about 2.0 molar equivalents of 2-amino-4-chloropurine **8** in the presence of from about 1.0 to about 6.0 molar equivalents of a base (for example potassium carbonate or LiH or NaH or KH or NaOH or KOH or lithium diisopropylamide or $LiN(Si(CH_3)_3)_2$ and the like) in an inert solvent (for example DMF or THF or acetonitrile or N-methylpyrrolidone or ethanol and the like) at a temperature of from about -25°C to about 140°C provides substituted purine **20**.

Alternatively, Mitsunobu coupling (for example, $P(PH)_3$/diethyl azidocarboxylate) of alcohol **18** with 2-amino-4-chloropurine **8** provides **20**.

Reaction of **20** with from about 2.0 to about 20.0 molar equivalents of an alcohol R_9OH (R_9 is an alcohol protecting group such as benzyl or diphenylmethyl and the like) in the presence of from about 1.0 to about 6.0 molar equivalents of a base (for example, potassium t-butoxide or potassium carbonate or NaH or KH or lithium diisopropylamide and the like in an inert solvent (for example, THF or DMF and the like) at a temperature of from about -25°C to about 150°C provides alcohol **21**.

Removal of the alcohol protecting group R_9 of **21** (for example by catalytic hydrogenation in an inert solvent such as ethanol or benzyl alcohol or methanol or THF and the like in the presence of an hydrogenation catalyst such as Pd/C or $Pd(OH)_2$ and the like) provides substituted guanine **22**, which can be esterified as described in Scheme C (i.e., **11** to **12**) to provide **23**.

The ether substitutent of **23** is deprotected by reaction with a) a reducing agent (for example, HCO_2H and Pd/C and the like) wherein R_{12} is $-CH(Ph)_2$ or $-C(Ph)_3$, or b) a desilylating agent (for example Bu_4NF and the like) wherein R_{12} is $-Si(t\text{-}Bu)(Me)_2$ and the like to provide **13**.

Alcohol **13** can be converted to **I** as outlined in Scheme C.

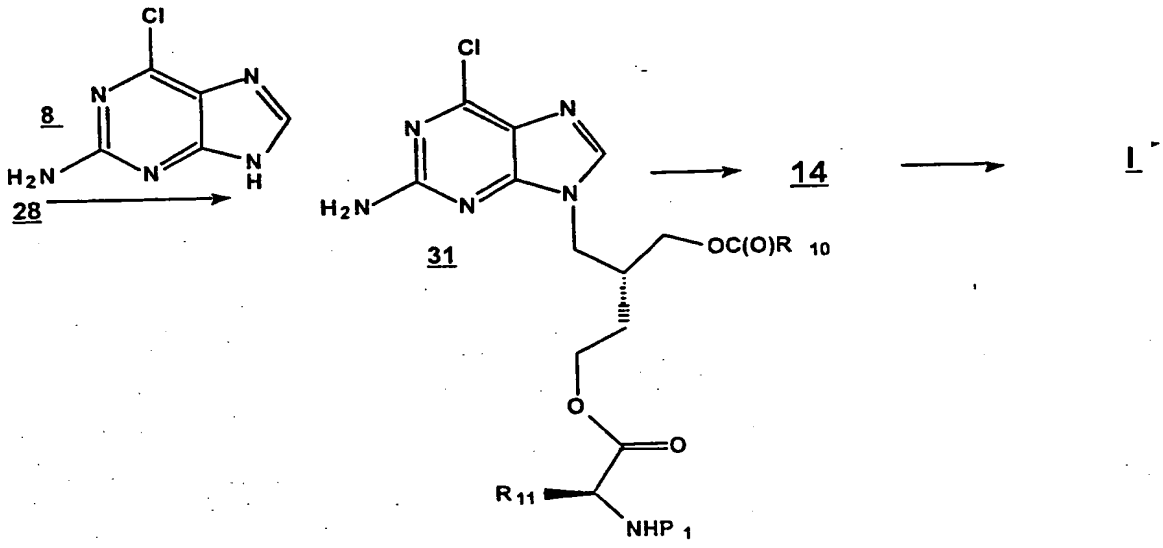
Yet another method for preparing compounds of Formula I is shown in Scheme E. Enzymatic esterification of **4** (see Scheme C) by reaction with from about 1.0 to about 20.0 molar equivalents of a vinyl ester **24** (R_{10} is C_3-C_{21} saturated or monounsaturated, optionally substituted alkyl) in the presence of a lipase (for example, Lipase PS-30 or Lipase PPL or Lipase CCL and the like) or a phospholipase (for example phospholipase D and the like) provides the desired stereoisomer of ester **25**. This reaction can be carried out in the absence of solvent or in the presence of an inert solvent (for example, methyl t-butyl ether or toluene or hexane and the like). The reaction is carried out at a temperature of from about -20°C to about 80°C.

The alcohol substituent of **25** is converted to a leaving group (for example, a halogen or a sulfonate) by reaction with a halogenating agent (for example NBS/$P(Ph)_3$ or NCS/$P(Ph)_3$ or $POCl_3$ or NCS/$P(Ph)_3$/NaI in acetone and like) in an inert solvent (for example, methylene chloride or toluene or ethylacetate and the like) or by reaction with from about 0.8 molar equivalents to about 2.0 molar equivalents of a sulfonyl halide (for example, benzenesulfonylchloride, toluenesulfonylchloride or methane sulfonylchloride and the like) in the presence of from about 1.0 to about 4.0 molar equivalents of a base (for example, triethylamine or potassium carbonate or pyridine or dimethylaminopyridine or ethyldiisopropylamine and the like) in an inert solvent (for example methylene chloride or toluene or ethylacetate or pyridine or methyl t-butyl ether and the like) at a temperature of from about -25°C to about 100°C to provide ester **26** (X_2 is a halogen or sulfonate leaving group).

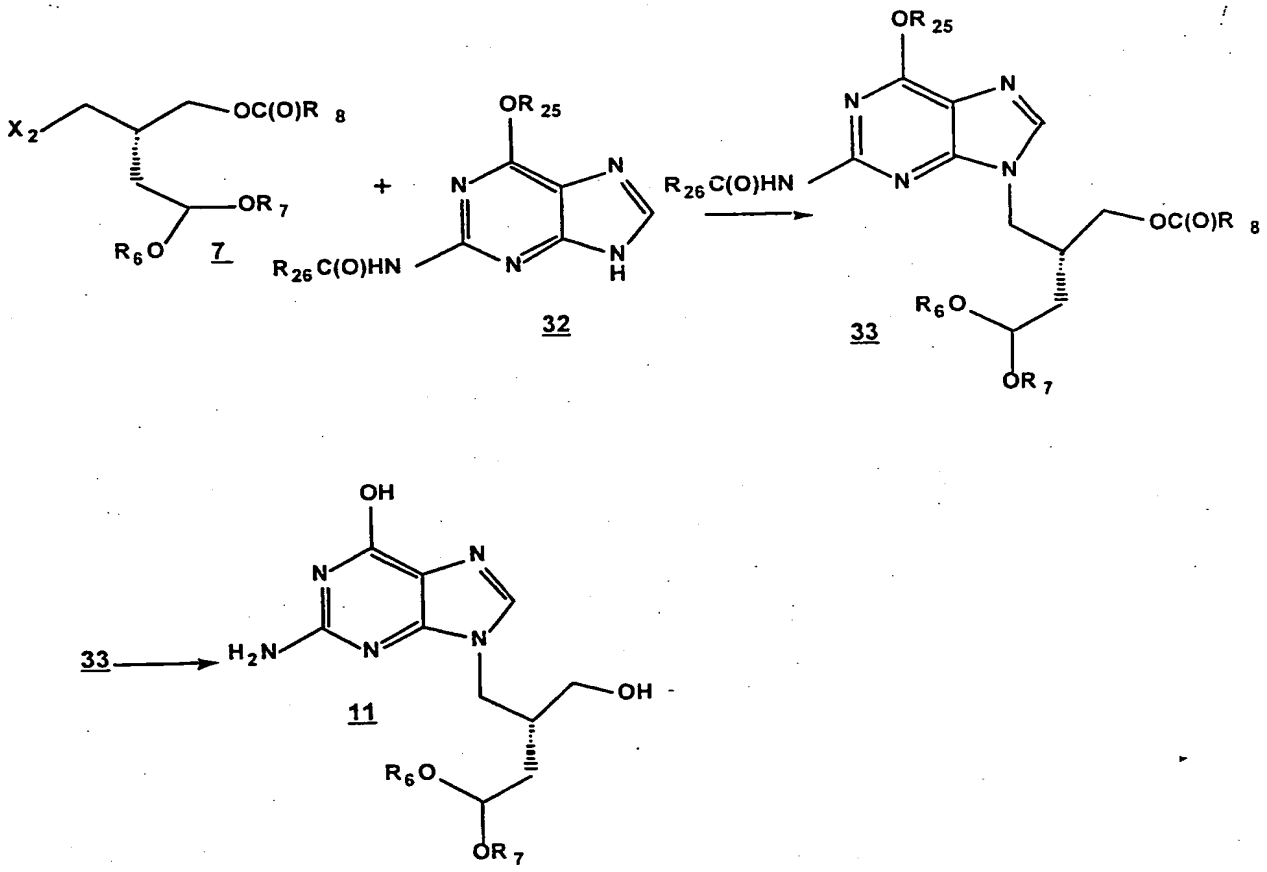
The acetal substituent of **26** is hydrolyzed to the aldehyde **27** by reacting **26** with an acid (for example, trifluoroacetic acid, triflic acid or HCl or formic acid or acetic acid/formic acid or sulfuric acid and the like) in an inert solvent (for example, THF/H_2O or methylene chloride/H_2O or ethylacetate/H_2O or ethanol/H_2O or methanol/H_2O or water and the like) at a temperature of from about -25 °C to about 100°C.

Alternatively, in the reaction of **28** with **29**, the base can be a sterically bulky amine base (for example, 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU), 1,4-diazabicyclo[2.2.2]octane (Dabco), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), tetramethylguanidine, N,N-diisopropylethylamine and the like) or a sterically bulky phosphazine base (for example, tert-butylimino-tri(pyrrolidino)-phosphorane, tert-butylimino-tri(dimethylamino)phosphorane, tert-octylimino-tri(dimethylamino)phosphorane and the like) in an inert solvent (for example, THF or DMF or DMSO and the like).

SCHEME F



SCHEME G



Yet another method for preparing the compounds of formula I is shown in Scheme G. Alkylation of **32** with **7** in the presence of a base (for example, potassium carbonate, LiH, NaH and the like) in an inert solvent (for example, DMF THF and the like) provides **33**. R_{25} is hydrogen or $-C(O)NR_{27}R_{28}$ wherein R_{27} and R_{28} are independently selected from loweralkyl, phenyl and benzyl or R_{27} and R_{28}, taken together with the nitrogen to which they are attached, form a pyrrolidinyl group or a piperidinyl group. R_{26} is loweralkyl, phenyl or benzyl.

Hydrolysis of **33** to **11** can be accomplished under basic conditions (for example, with KOH in water and the like).

methanol was removed by distillation and the distillation residue was diluted with distilled water (112 kg) and 9.2 kg of a 50% aqueous KOH solution. The resulting mixture was heated to reflux for 16 hours. The contents of the reactor were cooled to 25°C and were then adjusted to pH 7.0 using 37% aqueous acetic acid solution. The internal temperature of the reactor was then adjusted to 10°C and the contents stirred for 30 minutes. The resulting slurry was centrifuged and the resulting wet cake was charged back to the reactor. To the cake was charged distilled water (70 kg). The internal temperature was adjusted to 50°C and the contents were stirred for 30 minutes. Then the internal temperature was adjusted to 20°C and the contents stirred for 30 minutes. The resulting slurry was centrifuged and the cake rinsed once with distilled water (15 kg). The cake was transferred to dryer trays and dried at 45°C under vacuum for 18 hours to provide the desired product as a pale yellow powder (8.6 kg, 99% ee).

Example 2

Alternative preparation of (R)-9-[4-hydroxy-2-(stearoyloxymethyl)butyl]-guanine

To a 2 liter round bottom, 3-neck flask equipped with a nitrogen inlet, temperature probe, rubber septum and mechanical stirrer was charged stearic acid (25.0 g), THF (525 mL) and triethylamine (12.2 mL). The resulting solution was cooled to ^{3}0°C using an ice/salt bath. Pivaloyl chloride (10.3 mL) was added slowly via a syringe, maintaining the reaction temperature at less than 5°C. The resulting slurry was stirred at 0 ±5°C for 2 hours. The ice bath was removed and the reaction allowed to warm to room temperature. The resulting precipitate was filtered and the filter cake was rinsed with THF (100 mL). The resulting clear filtrate was added to a 3 liter 3-neck flask (equipped with a nitrogen inlet and mechanical stirrer) charged with the product of Example 1 (22.5 g) and DMAP (1.7 g). The reaction mixture was stirred overnight at room temperature. The reaction mixture was then cooled to 18°C and a room temperature solution of 1:1

The product of Example 31 c) of WO 98/34917 (6.00 g) was dissolved in THF (60 mL). Borane t-butylamine comlex (0.48 g) was added neat at room temperature. The reaction mixture was stirred at room temperature for 1.25 hours. The pH was adjusted to 7-8 by addition of 5% aqueous HCl. The reaction mixture was diluted with THF (60 mL) and was washed with 20% brine (40 mL) and then again with saturated brine (30 mL). The organic solution was filtered through a pad of silica gel, dried over magnesium sulfate (6.0 g) for one hour and filtered. The filtrate was added to the product of Example 37 a) of WO98/34917 (7.0 g) and DMAP (70 mg). The mixture was stirred under nitrogen at room temperature for about 3 hours. An additional amount of the product of Example 37 a) (0.5 g) was added and the mixture was stirred overnight at room temperature. An additional amount of the product of Example 37 a) (0.5 g) was added and the mixture was stirred overnight. The reaction mixture was diluted with ethyl acetate (90 mL) and washed with half-saturated sodium bicarbonate (90 mL), with brine (60 mL), with 5% KH_2PO_4 (60 mL) and brine (60 mL). The organic solution was dried over sodium sulfate and concentrated to provide the desired product as a yellow oil (6.88 g).

Example 4

(R)-2-Amino-6-chloro-9-[4-(N-benzyloxycarbonyl-L-valyloxy)-2-(stearoyloxymethyl)butyl]purine

A 100 ml round bott0m 3-neck flask was charged with lithium hydride (58 mg, 7.3 mmol) and DMF (10 mL). 2-Amino-6-chloropurine (1.14 g, 6.72 mmol) was added al at once at room temperature. The mixture was stirred at room temperature for 40 minutes under nitrogen. The product of Example 31 d) of WO98/34917 (5.2 g, 6.72 mmol) as a solution in DMF (10 mL) was added dropwise. After complete addition, the reaction mixture was stirred at 40-50°C under nitrogen for 27 hours. The reaction mixture was cooled to room

acetate and washed with water, aqueous sodium bicarbonate and bringe. The organic solution was evaporated under reduced pressure to give the desired product (134 mg).

Example 7

Alternative preparation of (R)-2-Amino-6-chloro-9-[4,4-diethoxy-2-(hydroxymethyl)butyl]purine

DBU (36.8 g, 0.24 mol) was added to a suspension of 2-amino-6-chloropurine (41 g, 0.24 mol) in DMF (340 mL) at room temperature under nitrogen. After 5 minutes, the product of Example 14 d) of WO98/43917 (85 g, 0.22 mol) was added. The mixture was stirred at 40-45°C for 15-20 hours. Then the mixture was diluted with methyl t-butyl ether (340 mL), toluene (340 mL), water (340 mL) and brine (340 mL). After mixing for 15 minutes, the organic layer was separated and the aqueous layer was extracted with toluene (2 x 300 mL). The combined organic layer was washed with water (500 mL) and concentrated under vacuum at 60°C bath temperature. The resulting oil was diluted with methanol (260 mL) and cooled to 5°C. A solution of K_2CO_3 (16 g, 0.12 mol) in water (65 mL) was added over 15 minutes maintaining the reaction mixture temperature below 10°C. The mixture was stirred at 10°C for 1 hour. Then the mixture was diluted with brine (500 mL) and stirred for 30 minutes. The resulting solid was filtered, washed with 5% methanol in water (50 mL) and the filter cake was dried to give the desired product as a white solid (39 g).

Example 8

Alternative preparation of (R)-2-Amino-6-chloro-9-[4,4-diethoxy-2-(acetoxymethyl)butyl]purine

Example 11

2-Amino-6-iodopurine

To a 2 liter single-neck round bottom flask with a mechanical stirrer was charged 2-amino-6-chloropurine (41.0 g, 242 mmol). The flask was cooled in an ice-water bath. The the reaction flask was charged HI (47% solution, pre-cooled in a refrigerator, 250 mL) in one portion. The resulting suspension was stirred for 16 hours at ice-water bath temperature. Water (500 mL) was charged to the reaction flask. The suspension was stirred at 0°C for 1 hour. The precipitate was filtered and washed with water (3 x 250 mL). The filter cake was transferred to a 250 mL filtration flask. 6 M NaOH solution (85 mL) was added to the solid through the filter to rinse out residual solid and wash into the filter flask. The solution obtained was added slowly to a boiling solution of acetic acid (25 mL) and water (250 mL). The resulting suspension was cooled to room temperature and stirred at room temperature for 2 hours. The solid was collected by centrifugation, washed with water (2 x 250 mL), followed by heptane (250 mL). The solid was first spin-dried on the centrifuge for 30 minutes and then dried in a vacuum oven overnight to provide the desired product (61.3 g).

Example 12

Alternative preparation of (R)-9-[4-(N-benzyloxycarbonyl-L-valyloxy)-2-(stearoyloxymethyl)butyl]guanine

a) (R)-2-Amino-6-iodo-9-[4-(N-benzyloxycarbonyl-L-valyloxy)-2-(stearoyloxymethyl)butyl]purine

To a 50 mL single neck round bottom flask was charged the product of Example 31 d) of WO98/34917 (2.0 g, 2.58 mmol), 2-amino-6-iodopurine (0.742 g, 2.84 mmol), DBU (o.425 mL) and DMF (10 mL). The reaction mixture was

evaporation of the solvent each time under reduced pressure, to provide a solid. The solid was recrystallized from refluxing acetonitrile (50 mL). After cooling the acetonitrile mixture to room temperature, it was allowed to stand at room temperature overnight and then was cooled to -13°C for 30 minutes. The resulting solid was collected by filtration, washed with acetonitrile (2 x 10 mL) and dired in a vacuum oven to provide the desired product (2.4 g).

Example 13

(R)-2-Amino-6-iodo-9-[4,4-diethoxy-2-(acetoxymethyl)butyl]purine

To a 100 mL single neck round bottom flask was charged the product of Example 14 d) of WO 98/34917 (9.3 g, 23.9 mmol), 2-amino-6-iodopurine (4.8 g, 18.4 mmol), DBU (3.6 mL, 24.0 mmol) and DMF (50 mL). The mixture was stirred for 16 hours at 45°C. The reaction mixture was cooled to room temperature and ethyl acetate (250 mL) was added and stirring continued for 30 minutes. The reaction mixture was filtered and the filtered solid was washed with ethyl acetate (2 x 125 mL). The filtrate and washings were combined and washed with water (4 x 50 mL). The organic solution was evaporated under reduced pressure. Ethyl acetate (50 mL) was added to the residue and evaporated under reduced pressure. Methyl t-butyl ether (300 mL) was added to the residue and stirred. The resulting solid was filtered and dried to provide the desired product (8.8 g).

(K_2CO_3 can be used in place of DBU in the above procedure to provide the desired product).

^{1}H NMR (300 MHz, $CDCl_3$): 7.81 (s, 1H), 5.12 (br s, 2H), 4.61 (t, 1H), 4.16 (m, 1H), 4.04 (m, 2H), 3.62 (m, 2H), 3.48 (m, 2H), 2.52 (m, 1H), 2.03 (s, 3H), 1.79 (s, 1H), 1.69 (m, 2H), 1.19 (m, 6H).

balloon was replaced with a condenser and the reaction mixture was heated to 65°C for 25 minutes. The reaction mixture was then filtered through celite (6.05 g) and the filter cake was washed with isopropanol/THF (4/1, 2 x 50 mL). The filtrate was concentrated under vacuum (bath temperature 45°C) and residual THF was chased with isopropanol (50mL).

To the flask was added isopropanol (50 mL) and the mixture was heated to about 80°C to dissolve the solids. Isopropyl acetate (150 mL) was added and heating was continued to dissolve the solid which formed. Once all solids were dissolved, the solution was cooled to room temperature and stirred for 12 hours. The resulting solid was filtered and dried to provide a light gray solid (9.0 g). This solid was added to a 500 mL round bottom flask, along with activated carbon (2.25 g) and isopropanol (200 mL). The mixture was heated to 60-65°C for 1 hour and then filtered through celite (6.00 g). The celite cake was washed with hot isopropanol (65°C, 2 x 50 mL) and the filtrate was concentrated under reduced pressure (bath temperature of 50°C). Isopropanol (40 mL) was added to the residue and the mixture was heated to 80°C to dissolve the solids. Isopropyl acetate (120 mL) was added and heating was continued to dissolve the precipitate which formed. The solution was cooled to room temperature and stirred for 12 hours. The resulting solid was filtered and dried to give the desired product as a white solid (7.7 g).

Alternatively, the crude product of the hydrogenation reaction was mixed with isopropanol (50 mL) and the mixture was heated to 65-70°C to dissolve the solids. Acetonitrile (65 mL) was added dropwise via an addition funnel at a rate to maintain the temperature above 55°C. During addition of the acetonitrile, a fluffy gray precipitate formed. After addition of the acetonitrile was complete, the mixture was heated at 65°C for 30 minutes and then filtered through a pad of celite in a steam jacketed funnel. The filtrate was concentrated and residual acetonitrile was chased with isopropanol (70 mL). The resulting solid was recrystallized from isopropanol/isopropyl acetate (30/90 mL) and after stirring at

To the product of Example 15 a) (100 mg, 0.165 mmol) in a 25 mL round bottom flask was added KOH (62 mg, 0.972 mmol) and water (10 mL). The suspension was refluxed for 20 hours. The reaction mixture was cooled to room temperature and acidified to pH 5 using acetic acid. The solvent was evaporated under reduced pressure to provide the desired product as a white solid.

Example 16

2-N-Acetyl-(R)-9-[4,4-diethoxy-2-(acetoxymethyl)butyl]-guanine

To a 50 mL round bottom flask was added 2-N-acetyl-guanine (547 mg g, 2.83 mmol) and the product of Example 14 d) of WO98/34917(1.0 g, 2.6 mmol). Anhydrous DMSO (10 mL) was added, folowed by DBU (430 µL, 2.88 mmol). The resulting solution was stirred at 40°C under nitrogen for 24 hours. After cooling to room temperature, the reaction mixture was diluted with chloroform (50 mL) and water (20 mL). The organic layer was separated and washed with water (2x) and brine and then dried over sodium sulfate. The solvent was evaporated under vacuum to provide a light yellow oil, which was chromatographed on silica gel (10% methanol in ethyl acetate) to provide the desired product as a white foam (280 mg).

N-7 isomer:

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10-1.31 (m, 6H), 1.62-1.85 (m, 2H), 2.06 (s, 3H), 2.44 (s, 3H), 2.50-2.68 (m, 1H), 3.40-3.56 (m, 2H), 3.57-3.73 (m, 2H), 3.96-4.20 (m, 2H), 4.32-4.55 (m, 2H), 4.62 (t, J=5.5 Hz, 1H), 7.82 (s, 1H), 11.60 (s, 1H), 12.40 (s, 1H).

N-9 isomer:

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10-1.28 (m, 6H), 1.66-1.72 (m, 2H), 2.02 (s, 3H), 2.36 (s, 3H), 2.38-2.52 (m, 1H), 3.38-3.53 (m, 2H), 3.54-3.70 (m, 2H), 3.93-4.15

water (50 mL) and dried under vacuum at 50°C for 20 hours to provide the desired product as a pale yellow solid (24.3 g).

Example 19

Alternative preparation of (3S)-3-stearoyloxymethyl-4-toluenesulfonyloxy-butyraldehyde

To a 1 liter 3 neck round bottom flask equipped with a magnetic stirrer, temperature probe and nitrogen inlet was added the product of Example 31 b) of WO98/34917(40 g) and THF (320 mL). The solution was cooled to 20°C and a solution of trifluoromethane sulfonic acid (20 g) and water (20g) was added. After stirring for 2-3 hours, the reaction mixture was quenched with sodium bicarbonate (12.0 g), followed by addition of methyl t-butyl ether (500 mL). The organic layer was separated and washed with saturated aqueous sodium bicarbonate solution (200 mL), water (200 mL) and brine (200 mL) and then was dried over sodium sulfate. The organic solution was evaporated to dryness under vacuum to give a pale yellow oil which was dissolved in hexane (300 mL) and stirred overnight. The resulting solid was filtered and dried under vacuum to give the desired product as a white solid (25.6 g).

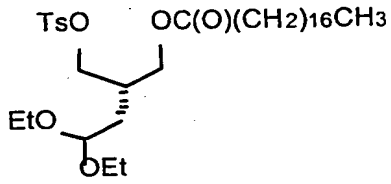
Example 20

Alternative preparation of (3S)-3-stearoyloxymethyl-4-toluenesulfonyloxy-butyraldehyde

To a 100 mL 3 neck round bottom flask equipped with a magnetic stirrer, temperature probe and a nitrogen inlet was added the product of Example 31 b) of WO98/34917 (6.5 g), acetic acid (30 mL) and formic acid (20 mL). After stirring at room temperature for 20 minutes, water (20 mL) was added to the mixture and stirring was continued at room temperature for 30 minutes. The

Heating and stirring was continued until the vinyl stearate was completely melted. Then the product of Example 14 b) of WO98/34917 (1800 g, 9.375 moles) and Lipase PS30 (45 g, 2.5 wt%) were added. The suspension was stirred at 35-37°C for 22 hours. The reaction mixture was quenched by addition of 37.5% methyl t-butyl ether in heptane (2.5 L). The mixture was then filtered through celite and the celite was washed with 37.5% methyl t-butyl ether in heptane (12 L). The organic filtrates were combined and washed with water (10 L) and 23% NaCl solution (10 L). The organic solution was evaporated and methylene chloride was aded (4 L). The solution was evaporated to about half of its original volume. An additional 4 L of methylene chloride was added and the solution was allowed to stand at 5°C overnight.

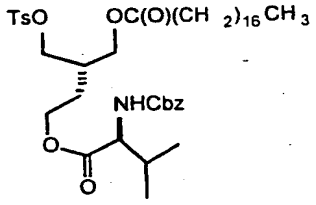
b) Preparation of (2S)-4,4-Diethoxy-2-stearoyloxymethyl-butyl toluenesulfonate.



The methylene chloride product solution resulting from Example 22 a) was added to a 50 L round bottom flask equipped with mechanical stirring, water condenser, nitrogen inlet and a temperature probe. An additional 4 L of methylene chloride was added, followed by triethylamine (2349 g, 23.2 moles) and p-toluenesulfonyl chloride (2654 g, 13.92 mol). The reaction mixture was stirred for 6 hours without external heating or cooling. Water (1.8 L) was added to the reaction mixture and stirred vigorously for 17 hours. The organic layer was separated and washed with water (10 L). The aqueous layer was extracted with

to slowly cool to 35°C, where cyrstallization occurs. The resulting thick mixture was stirred for 14 hours. The precipitate was filtered and rinsed twice with 4 L of heptane and then dried on the filter funnel for 2 hours and then in a vacuum oven with nitrogen purge for 60 hours at room temperature. The resulting solid (3200 g), heptane (30 L) and methyl t-butyl ether (1.6 L) were combined and heated with stirring to dissolution. The resulting solution was cooled over 1 hour to 42°C and the resulting suspension was stirred for 20 hours while cooling to room temperature. The precipitate was filtered and dried in a vacuum oven with nitrogen purge for 20 hours at room temperature to give the desired product (2860 g).

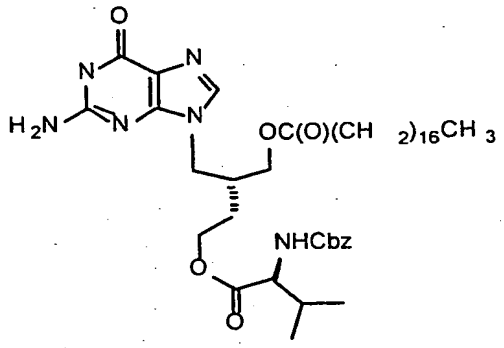
d) Preparation of (2S)-4-N-Carbonylbenzyloxy-L-valinyloxy-2-stearoyloxymethyl-butyl toluenesulfonate.



A solution of the product of Example 22 c) (511 g, 950 mmol) in THF (2.55 L) was stirred at ambient temperature in a high-pressure reactor with Raney Ni (383 g wet weight) under a 40 psi atmosphere of hydrogen for 2 hours. The suspension was filtered and the filtrate was swirled with magnesium sulfate (250 g) for 1 hour. The organic solution was filtered and added to N-Cbz-L-valine anhydride (598 g, 1.23 mol) and DMAP (5.8 g, 47.5 mmol) and stirred at ambient temperature for 20 hours. The reaction mixture was poured into 5% KH_2PO_4 (2.5 L) and extracted with methyl t-butyl ether (2.5 L). The organic layer was washed with 10% potassium carbonate (2 x 2.5 L) and then 23% NaCl solution (2.5 L). The volatiles were evaporated and methyl t-butyl ether (1 L) was added. The

ether/heptane.The filtrate was concentrated to provide the desired product (19.6 g).

f) Preparation of (R)-9-[(2-stearoyloxymethyl)-4-(N-benzyloxycarbonyl-L-valyloxy)butyl]guanine.



Into a 300 mL Fisher-Porter bottle (stirbar/nitrogen) was placed the product of Example 23 e) (12.36 g, 14.34 mmol) dissolved in acetonitrile (98 mL) and glacial acetic acid (98 mL), followed by addition of sodium acetate trihydrate (11.70 g, 86 mmol). The resulting mixture was stirred at 120°C for 4 hours. The mixture was cooled to room temperature and poured into 400 mL of methyl t-butyl ether. The mixture was washed with 5% aq. NaCl (2 x 300 mL), 2 M potassium carbonate (150 mL), 1% $NaHSO_3$ (100 mL) and brine (100 mL). The organic layer was concentrated under vacuum. The residue was dissolved in heptane (150 mL) and extracted with acetonitrile (2 x 100 mL). The top layer (heptane) was concentrated to give the desired product as a thick syrup (8.98 g).

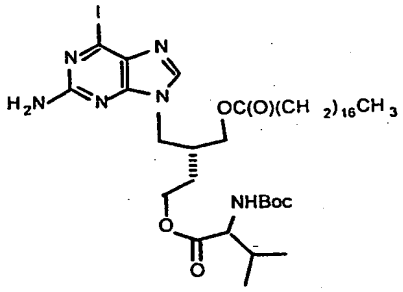
g) Preparation of (R)-9-[(2-stearoyloxymethyl)-4-(valyloxy)butyl]-guanine.

Into a 100 mL shaker was placed (R)-9-[(2-stearoyloxymethyl)-4-(N-benzyloxycarbonyl-L-valyloxy)butyl]guanine (4.53 g, 6.03 mmols) dissolved in

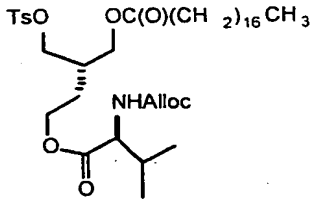
washed with 5% KH_2PO_4 (100 mL), 1 M potassium carbonate (100 mL) and then 27% NaCl solution (20 mL). The organic solution was then concentrated under vacuum to provide the desired product (3.67 g).

^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (m, 6H), 0.95 (d, 3H), 1.25 (m, 30 H), 1.45 (s, 9H), 1.55 (m, 2H), 1.70 (m, 2H), 2.1 (m, 1H), 2.21 (t, 2H), 2.46 (s, 3H), 3.94-4.2 (m, 6H), 5.0 (m, 1H), 7.37 (m, 2H), 7.78 (m, 2H). Mass Spec.=740 $(M+H)^+$

b) Preparation of 2-Amino-6-iodo-(R)-9-[(2-stearoyloxymethyl)-4-(N-t-butyloxycarbonyl-L-valyloxy)butyl]purine.



To a 100 mL flask equipped with a stir bar and a nitrogen inlet was added the product of Example 23 a) (3.67 g, 4.97 mmol), 2-amino-6-iodopurine (1.68 g, 6.46 mmol) and potassium carbonate (2.05 g, 14.9 mmol) slurried in DMF (27 mL). The resulting mixture was stirred for 16 hours at 50°C. The mixture was then cooled to room temperature and poured into 100 mL of ethyl acetate and washed with KH_2PO_4 (100 mL containing 20 mL of brine). The organic phase was washed with brine (2 x 75 mL), dried over magnesium sulfate, filtered and concentrated under vacuum. The residue was dissolved in acetonitrile (20 mL) at 50°C. The mixture was cooled to room temperature and stirred for 2 hours. The precipitate was filtered, washed with acetonitrile (2 x 5 mL) and dried to provide the desired product (2.79 g).



A solution of the product of Example 22 c) (15.0 g, 27.7 mmol) in THF (100 mL) was stirred at ambient temperature in a high-pressure reactor with Raney Ni (16 g wet weight) under a 5 psi atmosphere of hydrogen for 3 hours. The suspension was filtered and the filtrate was swirled with magnesium sulfate (8 g). The organic solution was filtered and N-Alloc-L-valine anhydride (13.82 g, 43.3 mmol) was added, followed by DMAP (0.203 g). The resulting mixture was stirred at ambient temperature overnight. The mixture was diluted with methyl t-butyl ether (120 mL) and was washed with 5% KH_2PO_4 (25 mL), 1 M potassium carbonate (100 mL) and then 27% NaCl solution (20 mL). The organic solution was then concentrated under vacuum to provide the desired product (20.6 g).

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (m, 6H), 0.95 (d, 3H), 1.25 (m, 30 H), 1.55 (m, 2H), 1.70 (m, 2H), 2.12 (m, 1H), 2.20 (t, 2H), 2.46 (s, 3H), 3.94-4.25 (m, 6H), 4.57 (m, 2H), 5.20-5.35 (m, 3H), 5.90 (m, 1H), 7.45 (m, 2H), 7.79 (m, 2H).

b) Preparation of 2-Amino-6-iodo-(R)-9-[(2-stearoyloxymethyl)-4-(N-allyloxycarbonyl-L-valyloxy)butyl]purine.

(2 x 15 mL), 2 M potassium carbonate (2 x 20 mL), 1% $NaHSO_3$ (2 x 15 mL) and brine (15 mL). The organic phase was concentrated under vacuum. The residue was chromatographed on silica gel (9/1 methylene chloride/methanol) to provide the desired product as a wax (0.67 g).

^1H NMR (300 MHz, d_6-DMSO): δ 0.85 (m, 9H), 1.21 (m, 30 H), 1.45 (m, 2H), 1.62 (m, 2H), 1.99 (m, 1H), 2.22 (t, 2H), 2.35 (m, 1H), 3.8-4.0 (m, 4H), 4.12 (t, 2H), 4.46 (m, 2H), 5.15-5.3 (m, 2H), 5.88 (m, 1H), 6.38 (b s, 2H), 7.63 (s, 1H), 10.52 (b s, 1H). Ic Mass Spec.=703 $(M+H)^+$

d) Preparation of (R)-9-[(2-stearoyloxymethyl)-4-(valyloxy)butyl]-guanine.

Into a 4 mL vial (stirbar/nitrogen) was added the product of Example 24 c) (0.07 g, 0.10 mmol) dissolved in THF (1.0 mL) and triphenylphosphine (1.6 mg) and $Pd_2(dba)_3$ (1.4 mg) and pyrrolidine (0.071 g). The resulting mixture was stirred at 25°C for 14 hours. The mixture was concentrated under vacuum, diluted with isopropanol and stirred at 4°C. The resulting precipitate was filtered to provide the desired product (33 mg).

Example 25

Diazobicycloundecenium Salts of 2-Amino-6-substituted-purines

Using a strong and neutral organic base capable of substantially compete deprotonation of a purine base allows *in situ* preparation of reasonably soluble purine salts. These are beneficial for synthetic purposes, being efficiently alkylated under relatively mild conditions. Advantageously, the salts of the invention are formed without the

or DMF at 40-45° with similar efficiency, but greater cleanliness as conventional tetrabutylammonium salts or purine in conjunction with K_2CO_3.

The respective 2-amino-6-substituted-purine (3 mmol), I,8-diazabicyclo[5.4.0]undecene (0.46 g, 3 mmol), and DMF (2.5 mL) or THF (5 mL) were mixed at room temperature for 0.5 h. The precipitate was filtered off, washed with (t-butyl methyl ether (10 mL), and dried under vacuum to give the salts indicated below:

Diazobicycloundecenium salt of 2-amino-6-chloropurine

90 % yield.

'H NMR (DMSO-d_6 δ): 1.5 - 1.7 (m, 6 H), 1.89 (m. 2 H), 2.68 (m, 2 H), 3.27 (m, 2 H), 3.43 (m, 2 H), 3.50 (m, 2 H), 5.69 (s, 2 H), 7.70 (s, 1 H).

^{13}C NMR (DMSO- d_6 δ): 19.1 (CH_2), 23.5 (CH_2), 26.1 (CH_2), 28.3 (CH_2), 31.7 (CH_2), 37.8 (CH_2), 47.8 (CH_2), 53.2 (CH_2), 126.2 (C), 145.1 (C), 153.4 (CH), 157.4 (C), 164.5 (C), 165.0 (C).

Diazobicycloundecenium salt of 2-amino-6-benzyloxypurine

80 % yield.

'NMR (DMSO-d_6 δ): 1.6 (m, 6H), 1.8 (m, 2 H), 2.5 (m, 2 H), 3.18 (m, 2 H), 3.25 - 3.4, (m, 4 H), 5.48 (s, 2 H), 5.93 (s. 2 H), 7.25 - 7.45 (m, 3 H), 7.5 (m, 2 H), 7.71 (s. 1 H).

^{13}C NMR (DMSO-d_6 δ): 19.8 (CH_2), 24.1 (CH_2), 26.6 (CH_2), 28.5 (CH_2), 32.5 (CH_2), 38.9 (CH_2), 47.7 (CH_2), 52.8 (CH_2), 66.4 (CH_2), 113.8 (C). 127.8 (CH), 128.3 (4C, CH), 137.2 (C), 143.5 (CH), 158.5 (C), 159.0 (C), 160.1 (C), 163.9 (C).

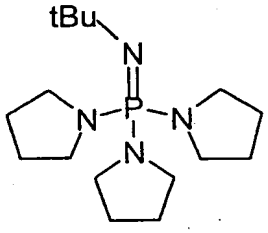
purine	Alkylating agent	solvent	Yield Σ N9 +N7	Ratio N9:N7
2-amino-6-chloropurine	A	DMF	79	4.1
2-amino-6-chloropurine	A	DMSO	85	4.0
2-amino-6-chloropurine	B	DMF	75	3.0
2-amino-6-chloropurine	B	DMSO	66	3.4
2-amino-6-BnO-purine	A	DMF	85	1.6
2-amino-6-BnO-purine	A	DMSO	81	1.7

A: (2S)-2-acetoxymethyl-4,4-diethoxybutyl toluenesulfonate

B: cyclopentyltosylate

Example 26

tert- Butyliminotri(pyrrolidino)phosphorane 2-amino-6-substituted purine salts



tert- Butyliminotri(pyrrolidino)phosphorane salts of various purines were prepared in situ by adding 1.1 g, 3.6 mmol of the bulky phosphorane depicted above to a slurry of 2-amino-6-substituted purine in THF (4 mL). The mixture was heated to 40 °C and stirred for 10 min without isolation of the salt.

'HNMR (DMSO-d_6 δ): 1.1 (m, 6 H), 1.55 (m, 2 H), 1.98 (s, 3 H), 2.45 (m, 1 H), 3.3 - 3.6 (m, 6 H), 3.95 (d, 2 H), 4.1 (d, 2 H), 4.5 (t, 1 H), 6.9 (s, 2 H), 8.15 (s, 1 H).
^{13}C NMR (DMSO-d_6 δ): 15.1 (2 C, CH_3), 20.5 (CH), 32.7 (CH_2), 33.9 (CH_3), 44.8 (CH_2), 60.6 (CH_2), 61.0 (CH_2), 64.2 (CH_2), 100.4 (CH), 123.2 (C), 143.5 (CH), 149.3 (C), 154.4 (C), 159.7 (C), 170.2 (C).
Anal. Calcd. for C16H24ClN504: C, 49.81; H, 6.27; N, 18.15. Found: C, 50.24, H, 6.41, N, 17.94.

(R)-2-amino-6-chloro-7-(2-acetoxymethyl-4,4,-diethoxybutyl)purine
'HNMR (DMSO-d_6 δ): 1.01(t, 7Hz, 3H), 1.04 (t, 7 Hz, 3 H) 1.42 - 1.67 (m, 2 H), 1.91 (s, 3 H), 2.40 (m, 1 H), 3.2 - 3.6 (m, 6 H), 3.95 (d, 5.1 Hz, 2 H), 4.3 (m, 2 H), 4.44 (t, 5.2 Hz. 1 H), 6.75 (s, 2 H), 8.35 (s, I H).
^{13}C NMR (DMSO-d_6 δ): 15.1 (2 C, CH_3), 20.5 (CH), 32.6 (CH_2), 35.0 (CH_3), 48.28 (CH_2), 60.6 (CH_2), 61.0 (CH_2), 64.2 (CH_2), 100.2 (CH). 114.9 (C), 142.2 (C), 149.9 (CH), 159.9 (C), 164.3 (C), 170.1 (C).

2-amino-6-chloro-9-cyclopentylpurine
^{1}NMR (DMSO-d_6 δ): 1.65 - 1.80 (m, 2 H), 1.82 - 2.09 (m, 4 H), 2.16 (m. 2 H), 4.76 (m, 1 H), 6.96 (s, 2 H), 8.27 (s, 1 H);

2-amino-6-chloro-7-cyclopentylpurine
'H NMR (DMSO-d_6 δ): 1.70 - 1.95 (m, 4 H), 1.95 - 2.1 (m, 2 H), 2.15 - 2.30 (m, 2 H), 5.11 (m, I H), 6.67 (s, 2 H). 8.53 (s, 1 H)

(R)-2-amino-6-benzyloxy-9-(2-acetoxymethyl-4,4,-diethoxybutyl)purine
'H NMR (DMSO-d_6 δ): 1.04 (t, 7.0 Hz, 3 H), 1.06 (t, 7.0 Hz, 3 H), 1.50 (m, 2 H), 1.98 (s, 3 H), 2.43 (m, 1 H), 3.3 - 3.6 (m, 6 H), 3.85 - 4.15 (m,

Table 2

purine	Alkylating agent	solvent	Yield Σ N9 +N7	Ratio N9:N7
2-amino-6-chloropurine	A	DMF	91	4.7
2-amino-6-chloropurine	A	DMSO	91	5.9
2-amino-6-chloropurine	*A, K_2CO_3*	*DMF*	*86*	*4.2*
2-amino-6-chloropurine	*A, tetrabutylN*	*DMF*	*86*	*5.0*
2-amino-6-chloropurine	B	DMF	80	3.8
2-amino-6-chloropurine	B	DMSO	83	4.8
2-amino-6-chloropurine	*A, K_2CO_3 [c]*	*DMF*	*59*	*3.3*
2-amino-6-chloropurine	*A, tetrabutylN[d]*	*DMF*	*75*	*3.7*
2-amino-6-BnO-purine	A	DMF	85	1.6
2-amino-6-BnO-purine	A	DMSO	81	1.7
2-amino-6-BnO-purine	*A, K_2CO_3[c]*	*DMF*	*57*	*1.1*

A: (2S)-2-acetoxymethyl-4,4-diethoxybutyl toluenesulfonate

B: cyclopentyltosylate

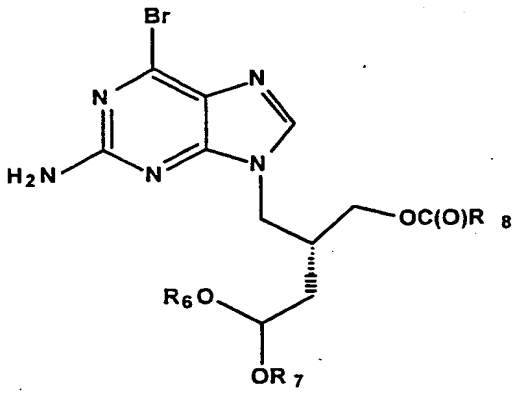
[c]: 1.85 equivalents of K_2CO_3

[d]: tetrabutylammonium salt

It will thus be apparent that the bulky phosphazine base provided superior regioisomeric control and yield with both alkylating agents used, compared to the conventional alkylation approaches of the purine in conjunction with a base (typically K_2CO_3) or a preformed and dried (due to the water byproduct formed during salt formation) tetrabutylammonium purine salt. It should also be noted that the bulky phosphazine base not only produced the purine salt in situ and without isolation, but also produced the cleanest reaction. The preparation of phosphazenium salt forming bases, otherwise known as Schwesingar bases is described in Schwesinger, R. Chimia 1985 39 269-272 and

Claims

1. A compound of the formula:



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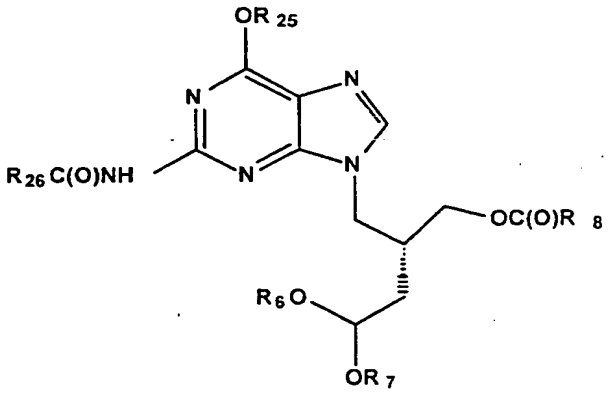

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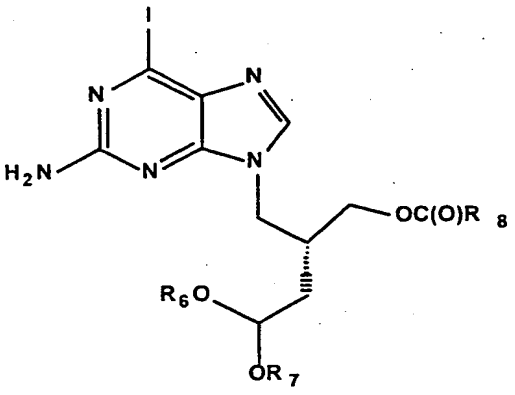
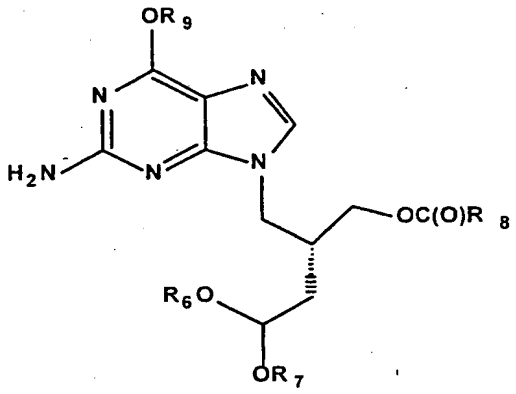
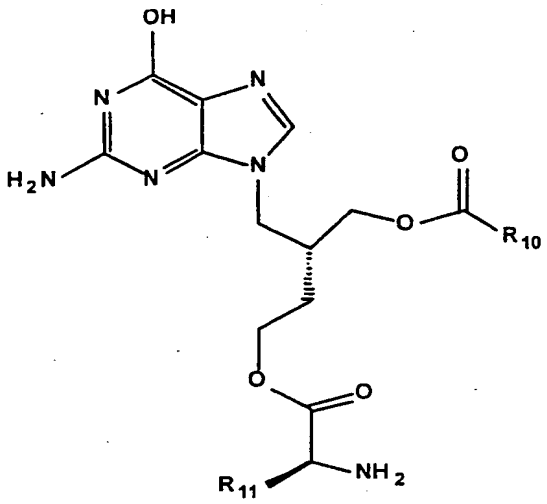


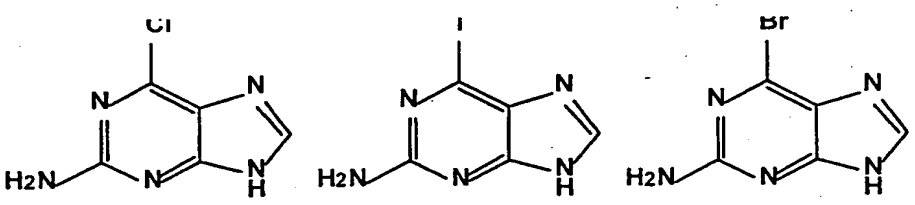
or

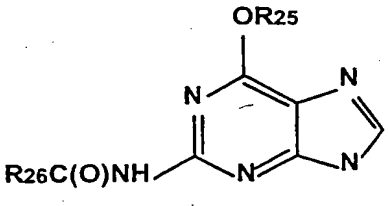


wherein R_6 and R_7 are loweralkyl or benzyl or R_6 and R_7 taken together are -CH_2CH_2-, -$CH_2CH_2CH_2$- or -$CH_2CH_2CH_2CH_2$-, R_8 is C_1-C_{21} saturated or monounsaturated, optionally substituted alkyl, R_9 is an alcohol protecting group, R_{25} is hydrogen or -$C(O)NR_{27}R_{28}$ wherein R_{27} and R_{28} are independently selected from loweralkyl, phenyl and benzyl or R_{27} and R_{28}, taken together with the nitrogen to which they are attached, form a pyrrolidinyl group or a piperidinyl group and R_{26} is loweralkyl, phenyl or benzyl.



wherein R_{10} is C_3-C_{21} saturated or monounsaturated, optionally substituted alkyl and R_{11} is isopropyl or isobutyl, comprising the step of reacting a compound of the formula:



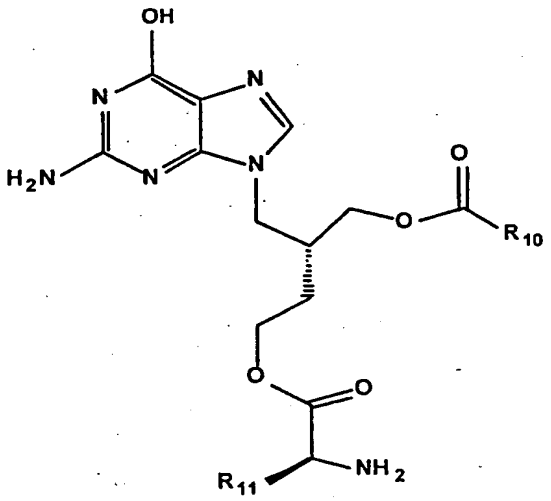


wherein R_{25} is hydrogen or -C(O)$NR_{27}R_{28}$ wherein R_{27} and R_{28} are independently selected from loweralkyl, phenyl and benzyl or R_{27} and R_{28}, taken together with

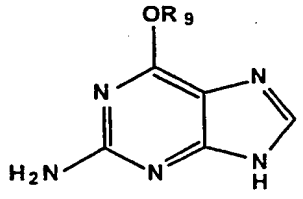
tri(dimethylamino)phosphorane, tert-butylimino-tri(pyrrolidino)-phosphorane and tert-octylimino-tri(dimethylamino)phosphorane.

14. A process according to claim 13, wherein the bulky phosphazine base is tert-butyliminotri(pyrrolidino)phosphorane.

15. A process for the preparation of a compound of the formula:

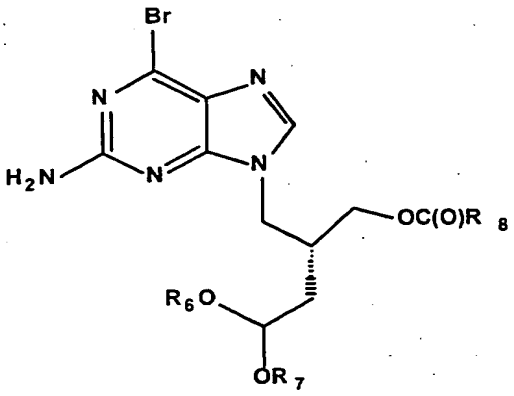


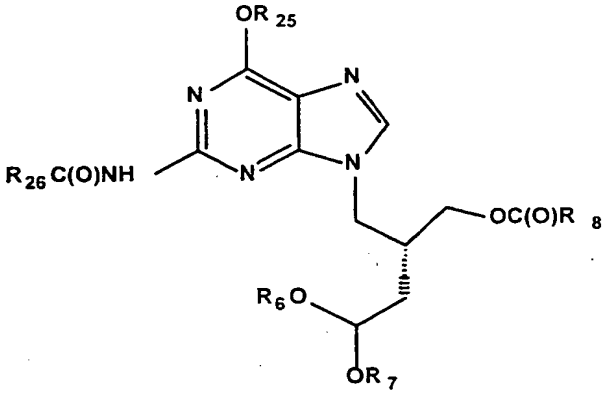
wherein R_{10} is C_3-C_{21} saturated or monounsaturated, optionally substituted alkyl and R_{11} is isopropyl or isobutyl, comprising the step of reacting a compound of the formula:

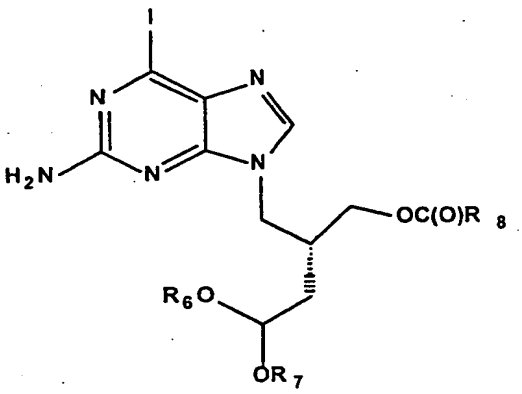


wherein R_9 is an alcohol protecting group with a compound of the formula:

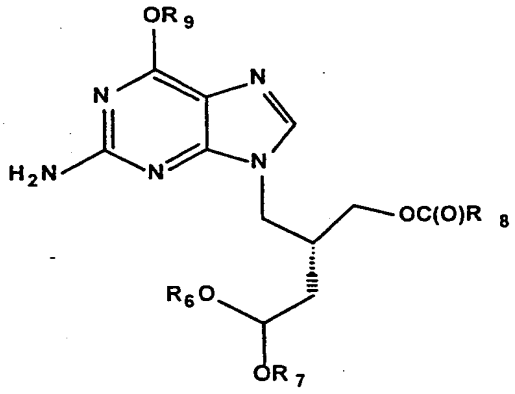
21. A process for the preparation of a compound of the formula:







or



wherein R_6 and R_7 are loweralkyl or benzyl or R_6 and R_7 taken together are -CH_2CH_2-, -$CH_2CH_2CH_2$- or -$CH_2CH_2CH_2CH_2$-, R_8 is C_1-C_{21} saturated or monounsaturated, optionally substituted alkyl, R_9 is an alcohol protecting group, R_{25} is hydrogen or -$C(O)NR_{27}R_{28}$ wherein R_{27} and R_{28} are independently selected from loweralkyl, phenyl and benzyl or R_{27} and R_{28}, taken together with the nitrogen to which they are attached, form a pyrrolidinyl group or a piperidinyl group and R_{26} is loweralkyl, phenyl or benzyl, comprising the step of reacting a compound of the formula:

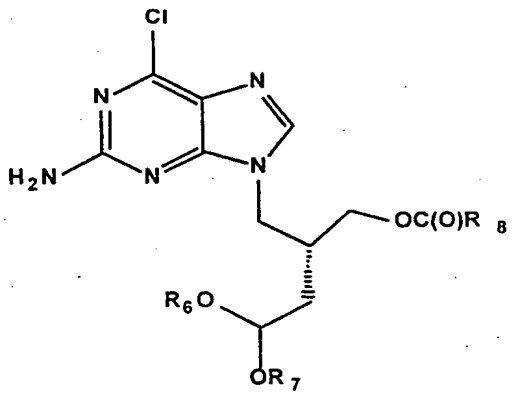
25. The process of Claim 24, wherein the base is potassium carbonate, LiH, NaH, KH, NaOH, KOH, lithium diisopropylamide, $LiN(Si(CH_3)_3)_2$ or a sterically bulky amine base.

26. The process of Claim 25, wherein the sterically bulky amine base is 1,8-diazabicyclo[5.4.0]undec-7-ene, 1,4-diazabicyclo[2.2.2]-octane, 1,5-diazabicyclo[4.3.0]non-5-ene, tetramethylguanidine, N,N-diisopropylethylamine or a sterically bulky phosphazine base.

27. The process of Claim 26, wherein the bulky phosphazine base is selected from the group consisting of tert-butylimino-tri(dimethylamino)-phosphorane, tert-butylimino-tri(pyrrolidino)phosphorane and tert-octylimino-tri(dimethylamino)phosphorane.

28. The process of Claim 27, wherein the bulky phosphazine base is tert-butyliminotri(pyrrolidino)phosphorane.

29. A process for the preparation of a compound of the formula:



wherein R_6 and R_7 are loweralkyl or benzyl or R_6 and R_7 taken together are -CH_2CH_2-, -$CH_2CH_2CH_2$- or -$CH_2CH_2CH_2CH_2$- and R_8 is C_1-C_{21} saturated or

32. The process of claim 31, wherein the bulky phosphazine base is tert-butyliminotri(pyrrolidino)phosphorane.

33. The process of Claim 29, wherein R_8 is $-(CH_2)_{16}CH_3$ or $-CH_3$ and X_2 is p-toluenesulfonyloxy.

34. A process for alkylating a purine base comprising reacting the purine with a sterically bulky phosphazine base prior to, or simultaneously with, addition of the alkylating agent.

35. A process according to Claim 34, wherein the purine is selected from 2-amino-6-halopurine or hydroxy-protected guanine.

36. A process according to Claim 35, wherein the purine-bulky phosphazine base reaction product is not isolated prior to alkylation.

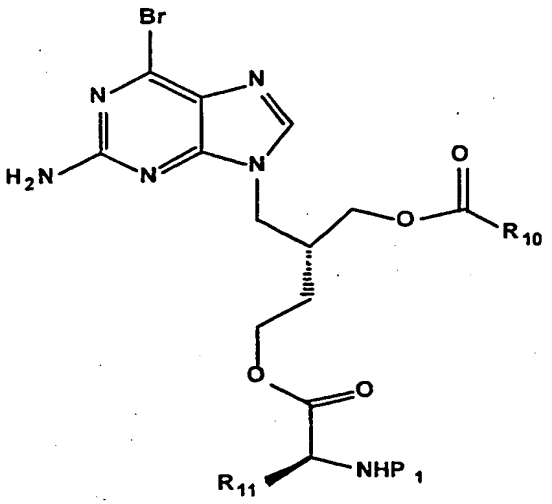
37. A process according to Claim 34, wherein the alklyating agent comprises a tosylate leaving group.

38. A process according to claim 34, wherein the alkylating agent comprises an optionally protected acyclic nucleoside side chain.

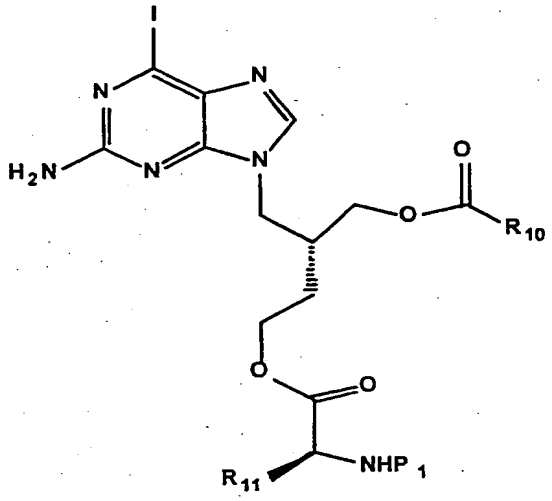
39. A process according to Claim 34, wherein the bulky phosphazine base is selected from the group consisting of tert-butylimino-tri(dimethylamino)phosphorane, tert-butylimino-tri(pyrrolidino)-phosphorane and tert-octylimino-tri(dimethylamino)phosphorane.

40. A process according to claim 39, wherein the bulky phosphazine base is tert-butyliminotri(pyrrolidino)phosphorane.

47. A compound of the formula:

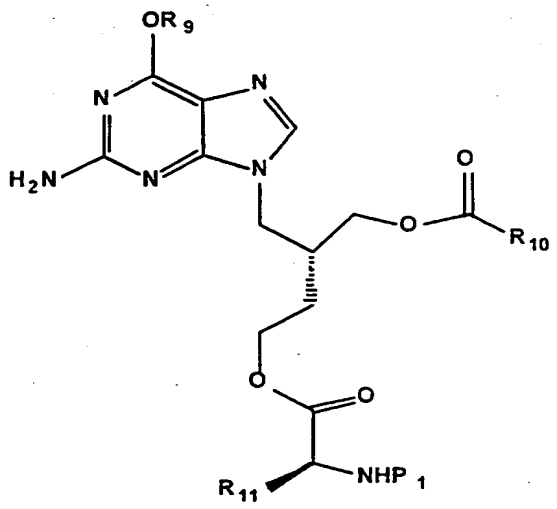


or



wherein R_{10} is C_3-C_{21} saturated or monounsaturated, optionally substituted alkyl, R_{11} is isopropyl or isobutyl and P_1 is an N-protecting group.

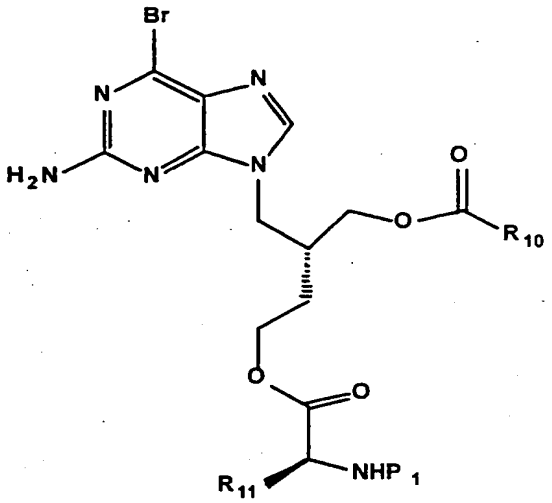
48. The compound of Claim 47, wherein R_{10} is $CH_3(CH_2)_{16}$-, R_{11} is isopropyl and P_1 is benzyloxycarbonyl, t-butyloxycarbonyl, allyloxycarbonyl or 2,2,2-trichloroethoxycarbonyl.



wherein R_9 is an alcohol protecting group, R_{10} is C_3-C_{21} saturated or monounsaturated, optionally substituted alkyl, R_{11} is isopropyl or isobutyl and P_1 is t-butyloxycarbonyl, allyloxycarbonyl or trichloroethoxycarbonyl.

52. The compound of Claim 51, wherein R_9 is benzyl, R_{10} is $CH_3(CH_2)_{16}$- and R_{11} is isopropyl.

53. A process for the preparation of a compound of the formula:



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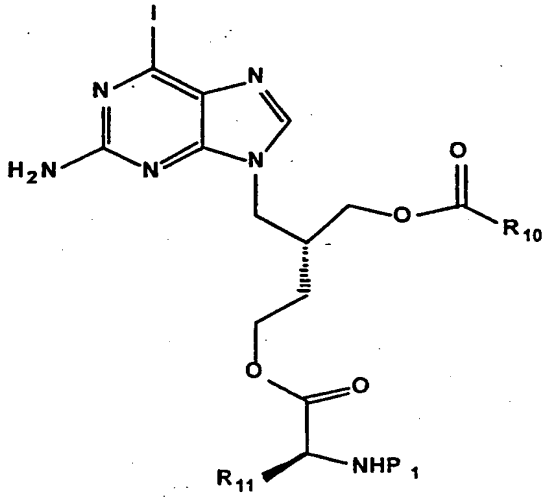
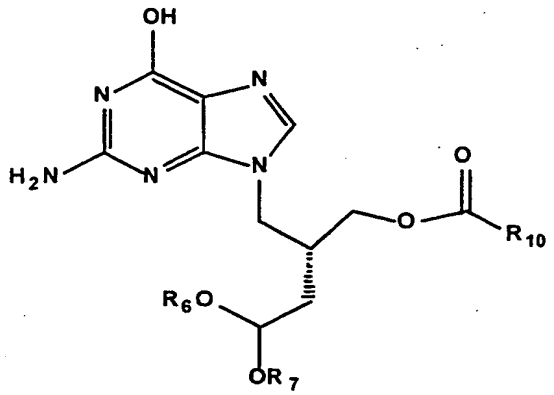


wherein R_{10} is C_3-C_{21} saturated or monounsaturated, optionally substituted alkyl, R_{11} is isopropyl or isobutyl and P_1 is an N-protecting group.

54. A process for preparing a compound of the formula:



wherein R_6, R_7 and R_{10} are defined as above,

b) deprotecting the acetal of the product of step a) and

c) reducing the aldehyde substituent of the product of step b),

characterized in that the products of steps a) and b) are not isolated.

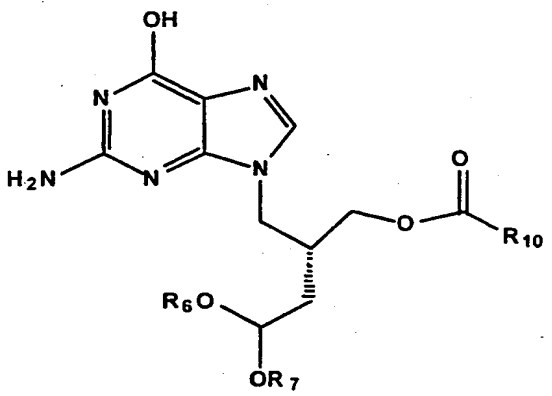
55. The process of Claim 54, wherein R_6 and R_7 are $-CH_2CH_3$ and R_{10}-is $-(CH_2)_{16}CH_3$.

56. The process of Claim 54, wherein the activated derivative of $R_{10}COOH$ is $CH_3(CH_2)_{16}C(O)OC(O)C(CH_3)_3$.

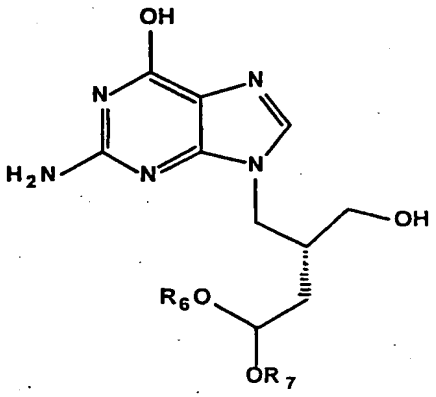
57. The process of Claim 54, wherein the acetal is deprotected with triflic acid and the aldehyde substituent of the product of step b) is reduced with borane t-butyl amine complex.

58. A process for preparing a compound of the formula:

61. A process for the preparation of a compound of the formula:



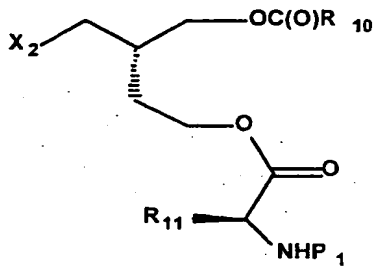
wherein R_6 and R_7 are loweralkyl or benzyl or R_6 and R_7 taken together are $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ or $-CH_2CH_2CH_2CH_2-$ and R_{10} is C_3-C_{21} saturated or monounsaturated, optionally substituted alkyl, comprising reacting a compound of the formula:



wherein R_6 and R_7 are as defined above with an activated derivative of $R_{10}COOH$, said activated derivative being prepared in situ.

wherein R_{10} and R_{11} are as defined above and P_1 is benzyloxycarbonyl with a hydrogenation catalyst selected from $Pd/BaSO_4$ and $Pd/BaCO_3$.

64. A compound of the formula:



wherein X_2 is p-toluenesulfonyloxy, R_{10} is $-(CH_2)_{16}CH_3$, R_{11} is isopropyl and P_1 is t-butyloxycarbonyl or allyloxycarbonyl.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/01339

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9408951 A1 (MONSANTO COMPANY), 28 April 1994 (28.04.94) --	13,14,19,20, 27,28,31,32, 39,40,42-43